Application of Functionalized Nanoparticles in Regulating Macrophage Polarization in Osteoarthritis

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Abstract. Osteoarthritis is a disease characterized primarily by chronic inflammation and joint degeneration, with a complex pathogenesis. Currently, there is no effective curative treatment. Macrophages play a key role in the inflammatory response and tissue repair in osteoarthritis, and the imbalance in their polarization is an important driving factor for the progression of the disease. Functionalized nanoparticles, with their high targeting ability and multifunctional properties, have shown great potential in regulating macrophage polarization, improving the inflammatory microenvironment, and promoting tissue repair. This paper reviews the role of functionalized nanoparticles in targeted delivery, signaling pathway regulation, and cytokine secretion, highlighting their mechanisms in modulating macrophage polarization. The paper systematically discusses the relationship between macrophage polarization and osteoarthritis, with a focus on preclinical experimental results. Functionalized nanoparticles have demonstrated significant therapeutic effects in alleviating inflammation, protecting cartilage, and promoting bone regeneration. Although there are still many challenges in terms of safety, targeting, and clinical translation, with the continuous development of nanotechnology, functionalized nanoparticles are expected to become an important breakthrough in the field of osteoarthritis treatment.

Keywords: Functionalized Nanoparticles; Macrophage Polarization; Osteoarthritis; Inflammation Regulation; Tissue Repair; Precision Medicine.

1. Introduction

Osteoarthritis is a common chronic joint disease, characterized by the gradual degeneration of articular cartilage, inflammation of the synovium, and the formation of bone spurs [1]. As the global population ages and lifestyles change, its incidence continues to rise, severely affecting the quality of life of patients [2]. While current treatments can alleviate symptoms, they are ineffective in halting disease progression and often have side effects. During the pathogenesis of osteoarthritis, macrophage polarization plays a dominant role, and its functional status significantly influences both inflammation and repair processes. M1 macrophages secrete pro-inflammatory cytokines that exacerbate cartilage degradation, while M2 macrophages secrete anti-inflammatory cytokines to promote tissue repair. However, in a chronic inflammatory environment, M1 macrophages become overactive, leading to prolonged inflammation and hindering repair [3].

Pharmacological interventions targeting macrophage polarization have several shortcomings. On one hand, traditional drug delivery methods fail to achieve precise targeting, leading to suboptimal drug concentrations at the site of injury and low drug efficacy [4]; on the other hand, certain lipophilic drugs struggle with solubility and stability issues, limiting their effectiveness.

The advent of functionalized nanoparticles offers a new hope in addressing these challenges [5]. By precise structural design and surface modification, nanoparticles can achieve targeted delivery, enhance therapeutic efficiency, and reduce systemic side effects. Nanoparticles can be modified with specific ligands to precisely target cells at inflammatory sites, releasing drugs or regulatory factors locally; they can also load functional molecules or drugs to directly influence macrophage polarization, improve the inflammatory environment, and promote tissue repair [7]. Compared with traditional methods, functionalized nanoparticles offer better targeting, biocompatibility, and degradability, enabling the slow release of active ingredients in the body and avoiding non-specific toxicity. This provides a new possibility for osteoarthritis treatment and holds the potential to become a significant breakthrough in this field [8].

2. Macrophage Polarization and Osteoarthritis

Macrophages are highly plastic immune cells that can differentiate into different subtypes based on microenvironmental stimuli, with M1 and M2 being the two primary types [9]. M1 macrophages are induced by lipopolysaccharide (LPS) and interferon-γ (IFN-γ), and they secrete a large number of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, enhancing local inflammatory responses and pathogen clearance. However, prolonged activation may lead to chronic inflammation and tissue damage [10]. M2 macrophages, on the other hand, differentiate under the influence of IL-4, IL-13, and other factors, secreting anti-inflammatory cytokines like IL-10 and TGF-β, and participating in tissue repair and fibrosis. Their formation requires key molecules like IL-4/IL-13/IL-10/IL-3, STAT3/6, IRF4, etc. [11].

In osteoarthritis, M1 macrophages are the main drivers of the inflammatory response. The pro-inflammatory cytokines and reactive oxygen species (ROS) they secrete promote chondrocyte apoptosis and matrix metalloproteinase (MMP) secretion [12], accelerating the degradation of the cartilage matrix. They also interact with synovial cells to maintain the chronic inflammatory environment. M2 macrophages play a protective role by secreting anti-inflammatory factors and participating in extracellular matrix remodeling to promote cartilage repair. However, the chronic inflammatory environment of osteoarthritis leads to a significant increase in M1 macrophage proportions, disrupting the M1/M2 balance and exacerbating inflammation and cartilage degeneration [13]. Regulating macrophage polarization towards the M2 type may alleviate the inflammatory response in arthritis, promote cartilage regeneration, and provide a new therapeutic strategy for osteoarthritis. Studying its polarization mechanism is crucial for uncovering the pathogenesis of the disease and developing new treatments.

3. Functionalized Nanoparticles in Regulating Macrophage Polarization

3.1 Targeting Modifications of Nanoparticles

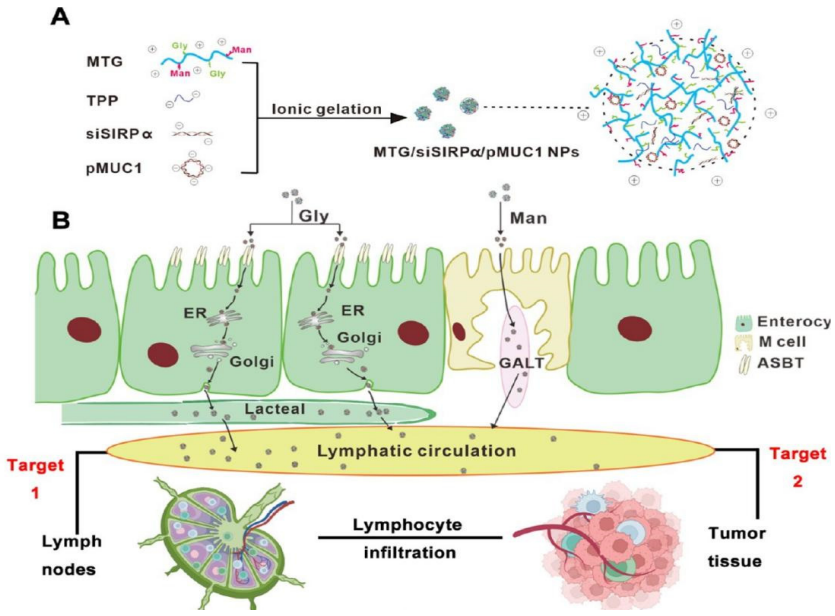

Figure 1. Schematic diagram of M1 and M2 macrophage polarization and their surface markers.

Xu L, Weng S, Li S, Wang K, Shen Y, Xu Y, Tang C, Yin C. Engineering the Intestinal Lymphatic Transport of Oral Nanoparticles to Educate Macrophages for Cancer Combined Immunotherapy. ACS Nano. 2023 Jun 27;17(12):11817-11837. doi: 10.1021/acsnano.3c02985. Epub 2023 Jun 15. PMID: 37318192.

Macrophages, as key members of the immune system, have high plasticity and can differentiate into different subtypes based on environmental stimuli, with M1 and M2 being the two most

prominent types. M1 macrophages are the classic pro-inflammatory type, primarily involved in cell-mediated immune responses. They initiate and sustain the inflammatory response by secreting large amounts of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-12. The surface markers of M1 macrophages include CD80, CD86, iNOS, and MHC II [14]. These markers not only aid in identifying M1 macrophages but also provide a basis for targeted therapies.

In contrast to M1 macrophages, M2 macrophages are primarily involved in anti-inflammatory responses and tissue repair. They promote tissue repair by secreting anti-inflammatory cytokines like IL-10 and TGF-β. The surface markers of M2 macrophages include CD206 (mannose receptor), CD163, and Arg-1 (arginase-1) [15], which play important roles in immune regulation and suppression of excessive inflammation.

To precisely characterize the two polarization mechanisms of macrophages, as shown in Figure 1, macrophages differentiate into M1 and M2 types under different microenvironmental stimuli. M1 macrophages, as classical pro-inflammatory cells, secrete pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-12, and maintain the inflammatory response through surface markers CD80, CD86, iNOS, and MHC II. In contrast, M2 macrophages play a role in anti-inflammation and tissue repair by secreting anti-inflammatory cytokines such as IL-10 and TGF-β, and participate in immune regulation and inhibition of excessive inflammation through surface markers CD206, CD163, and Arg-1.

Understanding the surface markers of M1 and M2 macrophages is critical for nanoparticle-targeted therapy. Nanoparticles can be modified on their surface to combine with ligands that bind to corresponding receptors, enabling them to target specific types of macrophages [16]. For example, TCP-2 peptides can specifically recognize and bind to M1 macrophages by interacting with the scavenger receptors on M1 macrophages, achieving highly efficient targeting. L-arginine, as a ligand for M1 macrophage surface receptors [17], also has a significant role in targeting M1 macrophages. Mannose-modified nanoparticles can specifically bind to M2 macrophages and enhance their uptake, while the M2pep peptide is a peptide that specifically recognizes M2 macrophages.

Through these targeting modifications, nanoparticles can precisely deliver drugs to M1 or M2 macrophages, thereby playing important roles in inflammatory diseases, cancer immunotherapy, and tissue repair. For example, in an inflammatory mouse model, L-arginine-modified nanoparticles can significantly reduce inflammation and have good biocompatibility. Mannose-modified nanoparticles show good effects in the treatment of chronic inflammation and osteoarthritis.

3.2 Drug Encapsulation by Nanoparticles

3.2.1 Limitations of Conventional Drugs and Advantages of Nanoparticles

Conventional or free drugs face several disadvantages during delivery in the body. First, they lack sufficient targeting, causing drugs to distribute to non-target tissues, which lowers therapeutic efficacy and increases side effects. For instance, in the treatment of rheumatoid arthritis (RA), traditional anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids can alleviate inflammation symptoms [18], but their long-term use leads to gastrointestinal side effects and issues like osteoporosis. Second, some drugs have strong hydrophobicity, poor solubility, and instability, affecting their absorption and distribution in the body. Additionally, their bioavailability is low, resulting in the drugs being metabolized or cleared before reaching the target site.

The introduction of nanoparticles has effectively addressed these issues. By selecting and designing appropriate materials, as well as using effective drug encapsulation methods, nanoparticles not only improve the drug targeting and stability but also achieve sustained drug release [19]. The choice of materials and the design of functionalized nanoparticles are crucial for their anti-inflammatory effects. Common nanoparticle materials include synthetic polymers, natural polymers (such as chitosan and hyaluronic acid), metal and inorganic nanoparticles, etc. [20]. Each material has unique biocompatibility and biodegradability characteristics, and selecting the appropriate material is key to achieving anti-inflammatory effects.

Natural polymers like chitosan and hyaluronic acid are increasingly used to prepare functionalized nanoparticles due to their excellent biocompatibility and good degradability. Chitosan is a natural polymer extracted from the shells of shrimp and crabs [21], with abundant resources. In osteoarthritis treatment, these natural polymers effectively reduce immunogenic responses and toxic side effects, while the degradation products after macrophage uptake can effectively reduce local oxidative stress levels [22], alleviating inflammation. Studies show that nanoparticles made from chitosan and hyaluronic acid have strong immunoregulatory effects in inflammatory environments and can effectively inhibit M1 macrophage activation.

Synthetic polymers such as polyvinyl alcohol (PVA) and poly(lactic-co-glycolic acid) (PLGA) have the advantage of controlling nanoparticle size, surface charge, and drug release characteristics by adjusting the synthesis process and chemical structure [23], thereby optimizing therapeutic effects. PLGA, a widely used biodegradable material, can effectively deliver anti-inflammatory drugs in osteoarthritis treatment, and its degradation products cause minimal tissue irritation.

3.2.2 Methods of Nanoparticle Drug Encapsulation and Advantages

There are various methods for encapsulating drugs in nanoparticles, including:

Mesoporous nanoparticles, with their abundant pores, can encapsulate drugs in their internal voids, achieving high drug loading efficiency. This structure not only increases the drug loading capacity but also controls the drug release rate. For example, certain mesoporous silica nanoparticles can effectively encapsulate anti-inflammatory drugs [24], such as IKK inhibitors. By controlling pore size and surface modification, they achieve slow drug release, prolonging the duration of the drug's action.

Liposome nanoparticles, with their lipophilic structure, can encapsulate lipophilic drugs, improving their solubility and stability. For instance, certain lipid nanoparticles can effectively encapsulate fat-soluble drugs like vitamin D, enhancing their stability and bioavailability in the body [25]. This encapsulation method is especially useful for drugs that are unstable in aqueous solutions or have poor solubility, significantly improving their therapeutic efficacy.

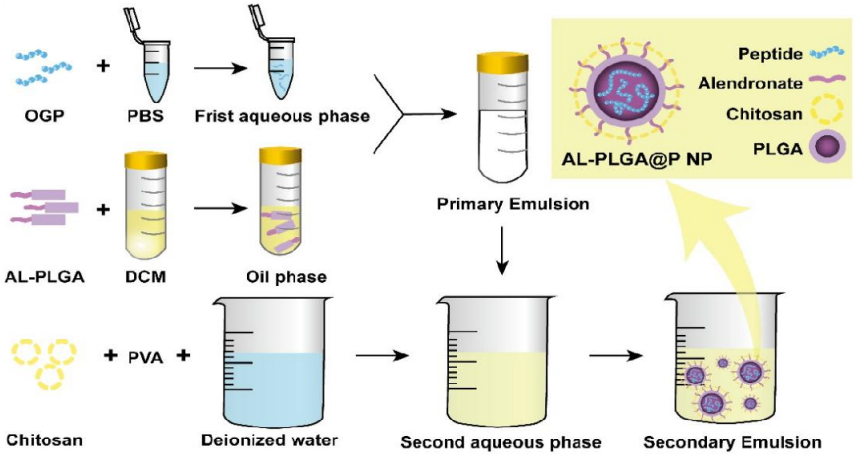

Figure 2. Schematic diagram of different methods for drug encapsulation in nanoparticles.

Ma S, Xu S, Li M, Du Y, Tian G, Deng J, Zhang W, Wei P, Zhao B, Zhang X, Liu Z, Wang Y. A Bone Targeting Nanoparticle Loaded OGP to Restore Bone Homeostasis for Osteoporosis Therapy. Adv Healthc Mater. 2023 Oct;12(25): e2300560. doi: 10.1002/adhm.202300560. Epub 2023 Aug 18. PMID: 37562069.

As shown in Figure 2, there are currently three main methods for drug encapsulation in nanoparticles. The first method involves the use of mesoporous nanoparticles. Mesoporous nanoparticles have abundant pores that can encapsulate drugs within their internal voids. This structure not only increases the drug loading capacity but also allows for regulation of the pore size and surface modifications to control the drug release rate. In this way, drugs can be released slowly, extending their duration of action in the body. The figure demonstrates the application of certain

mesoporous silica nanoparticles in encapsulating anti-inflammatory drugs (such as IKK inhibitors). The second method involves the use of lipid nanoparticles. The lipophilic structure of lipid nanoparticles allows them to effectively encapsulate lipophilic drugs, improving their solubility and stability. For example, certain lipid nanoparticles can effectively encapsulate fat-soluble drugs like vitamin D, enhancing their stability and bioavailability in the body. This method is particularly useful for drugs that are unstable or poorly soluble in aqueous solutions, significantly improving their therapeutic effect. Lastly, drugs can be encapsulated in nanoparticles via chemical modification. Drugs can bind to nanoparticles through physical adsorption or chemical bonding. Physical adsorption is suitable for small molecule drugs and hydrophilic drugs, where drugs are fixed on the nanoparticle surface via electrostatic adsorption or hydrophobic interactions. However, physical adsorption can lead to premature drug release in the bloodstream, affecting the therapeutic effect. In contrast, chemical bonding provides a more stable method for drug encapsulation by covalently bonding the drug to the nanoparticle surface, ensuring the drug's sustained and stable release in the body. This method not only extends the drug's circulation time but also improves its targeting and efficacy.

By chemical modification, drugs can be anchored to nanoparticles through physical or chemical bonds. Physical adsorption is suitable for small molecule drugs and hydrophilic drugs, where electrostatic or hydrophobic interactions fix the drugs on the surface of nanoparticles. This approach is simple but may lead to premature drug release in circulation, reducing the therapeutic effect. Chemical bonding, on the other hand, is a more stable method of drug loading [26]. Through covalent bonding, drugs can be securely attached to the nanoparticle surface, ensuring their sustained release in the body. For example, drugs linked to nanoparticles through covalent bonds not only prolong the drug's circulation time but also enhance its targeting and efficacy.

The advantages of drug-loaded nanoparticles are significant, mainly including the following points:

Through surface modification, nanoparticles can precisely target M1 or M2 macrophages, reducing the impact on normal tissues. For example, PEG modification can reduce non-specific binding with serum proteins, avoiding non-specific recognition and clearance by the immune system [27]. This targeting not only enhances the therapeutic effect of the drugs but also reduces their distribution in non-target tissues, minimizing side effects.

Nanoparticles can protect drugs from enzymatic degradation in the body, improving their stability and half-life. For instance, PLGA nanoparticles can effectively protect the encapsulated drugs [28], extending their circulation time in the body. This protective effect is particularly important since many drugs are easily degraded or metabolized in the body, reducing their efficacy. The protection provided by nanoparticles ensures that the drugs remain active when they reach the target site.

By designing nanoparticles properly, drugs can be released slowly, extending their action time and improving the therapeutic effect. For example, in chronic inflammatory diseases (such as rheumatoid arthritis), nanoparticles loaded with IKK inhibitors can significantly reduce the activation of M1 macrophages [29], decrease the release of inflammatory factors, and enhance the duration of the treatment. This sustained release effect not only improves the therapeutic outcomes but also reduces the frequency of administration, enhancing patient compliance.

In summary, nanoparticles, through careful material selection and design, along with effective drug encapsulation methods, not only enhance the targeting and stability of drugs but also enable sustained release, providing a new therapeutic strategy for treating various immune-related diseases. These advantages make nanoparticles highly promising in the field of drug delivery, especially in the treatment of chronic inflammatory diseases and cancer, demonstrating enormous potential.

3.3 How Drug-loaded Nanoparticles Regulate Macrophage Polarization After Entering the Body

After entering the body, drug-loaded nanoparticles release drugs through various mechanisms, thereby regulating macrophage polarization. Macrophages play a crucial role in osteoarthritis, and their immune regulatory functions in the joints are mainly achieved through the M1 and M2

polarization states [30]. M1 macrophages are typically pro-inflammatory and secrete large amounts of pro-inflammatory cytokines, exacerbating tissue damage, while M2 macrophages primarily exert anti-inflammatory and tissue repair functions.

During the inflammatory process of osteoarthritis, M1 macrophages activate signaling pathways such as NF-κB, MAPK, and JAK/STAT, promoting the release of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β) and matrix metalloproteinases (such as MMP-13) [31], leading to cartilage degradation and further disease progression. In contrast, M2 macrophages secrete anti-inflammatory cytokines (such as IL-10, TGF-β) and tissue repair-promoting factors (such as VEGF, FGF), which help reduce inflammation and promote cartilage repair.

Functionalized nanoparticles, through surface modifications with specific ligands (such as mannose, peptides, antibody fragments, etc.), can precisely target macrophage surface receptors, inducing polarization towards the M2 type and exerting anti-inflammatory and repair effects. For example, mannose-modified nanoparticles can bind specifically to the mannose receptors on M2 macrophages, promoting their anti-inflammatory functions and inhibiting M1 macrophage activity, reducing the secretion of pro-inflammatory factors [32]. Additionally, nanoparticles loaded with NF-κB inhibitors can effectively interfere with the pro-inflammatory pathways of M1 macrophages, further reducing the inflammation response.

Moreover, some nanoparticles, such as manganese-doped cerium oxide nanoparticles, can regulate macrophage polarization towards the M2 type through their antioxidant properties. The cytokines secreted by M2 macrophages promote osteoblast precursor cell differentiation, as well as positively regulate mineralization and angiogenesis. Experimental results have shown that these nanoparticles exhibit good catalase activity, generating oxygen from hydrogen peroxide and effectively reducing reactive oxygen species (ROS) within macrophages, guiding their polarization towards the M2 type.

4. Application of Functionalized Nanoparticles in Osteoarthritis

4.1 Alleviating Inflammation and Oxidative Stress in Osteoarthritis

Functionalized nanoparticles show significant potential in alleviating inflammation and oxidative stress in osteoarthritis. Their mechanisms mainly involve regulating macrophage polarization, inhibiting inflammatory responses, and improving the joint microenvironment. The chronic inflammatory response in osteoarthritis (OA) is primarily caused by the overactivation of macrophages, especially M1 macrophages, in the joint cavity. These M1 macrophages secrete large amounts of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β) and matrix metalloproteinases (such as MMP-13), which aggravate the degradation of joint cartilage and drive disease progression [33]. Functionalized nanoparticles can precisely regulate macrophage polarization, not only directly inhibiting inflammation but also reducing oxidative stress, improving the joint microenvironment, and ultimately alleviating osteoarthritis symptoms.

4.1.1 Mechanisms of Functionalized Nanoparticles in Regulating Macrophage Polarization

Macrophages play a critical role in osteoarthritis, with their immune regulation in the joint achieved through the two polarization states, M1 and M2. M1 macrophages are typically pro-inflammatory and secrete large amounts of pro-inflammatory factors, exacerbating tissue damage [34], while M2 macrophages mainly exert anti-inflammatory and tissue repair effects.

During the inflammatory process of osteoarthritis, M1 macrophages activate signaling pathways such as NF-κB, MAPK, and JAK/STAT, promoting the release of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β) and matrix metalloproteinases (such as MMP-13) [35], leading to cartilage degradation and further disease deterioration. Conversely, M2 macrophages secrete anti-inflammatory cytokines (such as IL-10, TGF-β) and tissue repair factors (such as VEGF, FGF), reducing inflammation and promoting cartilage repair.

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4.1.2 Material Selection and Design of Functionalized Nanoparticles

The material selection and design of functionalized nanoparticles have a significant impact on their anti-inflammatory effects. Common nanoparticle materials include synthetic polymers, natural polymers (such as chitosan, hyaluronic acid, etc.), metal, and inorganic nanoparticles [37]. Each material has unique biocompatibility and biodegradability characteristics, and selecting the appropriate material is crucial for achieving anti-inflammatory effects.

Natural polymers, such as chitosan and hyaluronic acid, are increasingly used to prepare functionalized nanoparticles due to their excellent biocompatibility and good biodegradability. Chitosan, a natural polymer extracted from shrimp and crab shells, is abundant in resources. In osteoarthritis treatment, these natural polymers can effectively reduce immunogenic responses and toxic side effects, and their degradation products, after macrophage uptake, can effectively reduce local oxidative stress levels [38], alleviating inflammation. Studies show that nanoparticles made from chitosan and hyaluronic acid have strong immunoregulatory effects in inflammatory environments and can effectively inhibit M1 macrophage activation.

Synthetic polymers, such as polyvinyl alcohol (PVA) and poly(lactic-co-glycolic acid) (PLGA), have the advantage of controlling nanoparticle size, surface charge, and drug release characteristics by adjusting the synthesis process and chemical structure [39], thereby optimizing therapeutic effects. PLGA, a widely used biodegradable material, can effectively deliver anti-inflammatory drugs in osteoarthritis treatment, and its degradation products cause minimal tissue irritation.

4.1.3 Mechanisms of Functionalized Nanoparticles in Regulating Inflammation and Oxidative Stress

Functionalized nanoparticles, through the regulation of macrophage polarization, not only reduce inflammation but also effectively alleviate oxidative stress, which is crucial for osteoarthritis treatment. Oxidative stress is an important pathological process in osteoarthritis, where the accumulation of free radicals, reactive oxygen species (ROS), and other substances exacerbates cartilage degradation and inflammation [40].

Interplay Between Oxidative Stress and Inflammation: Oxidative stress exacerbates inflammation by activating signaling pathways such as NF-κB, MAPK, and JAK/STAT, and conversely, the release of inflammatory cytokines (such as TNF-α, IL-6) increases ROS production, forming a vicious cycle [41]. Therefore, reducing oxidative stress and inflammation is an effective strategy to alleviate osteoarthritis. Functionalized nanoparticles can intervene in these signaling pathways to effectively alleviate inflammation and oxidative stress.

Relationship Between Macrophage Polarization and Oxidative Stress: The activation of M1 macrophages is a major source of oxidative stress. M1 macrophages not only secrete pro-inflammatory factors but also exacerbate oxidative stress by generating ROS and hydrogen peroxide. In contrast, M2 macrophages alleviate oxidative stress by secreting antioxidant factors (such as IL-10, TGF-β) [42]. Therefore, functionalized nanoparticles can significantly reduce oxidative stress levels by inducing M1 macrophages to polarize towards the M2 type, thereby improving joint health.

Surface-modified Nanoparticles: The surface modifications of nanoparticles determine their interaction with immune cells, particularly with macrophages. For instance, mannose-modified nanoparticles can target M2 macrophages, inducing these cells to secrete antioxidant factors, thereby inhibiting oxidative stress. Studies have shown that mannose-modified nanoparticles accumulate in the synovial tissue, effectively reducing ROS production and inhibiting cartilage matrix degradation. The specific situation is shown in Figure 3.

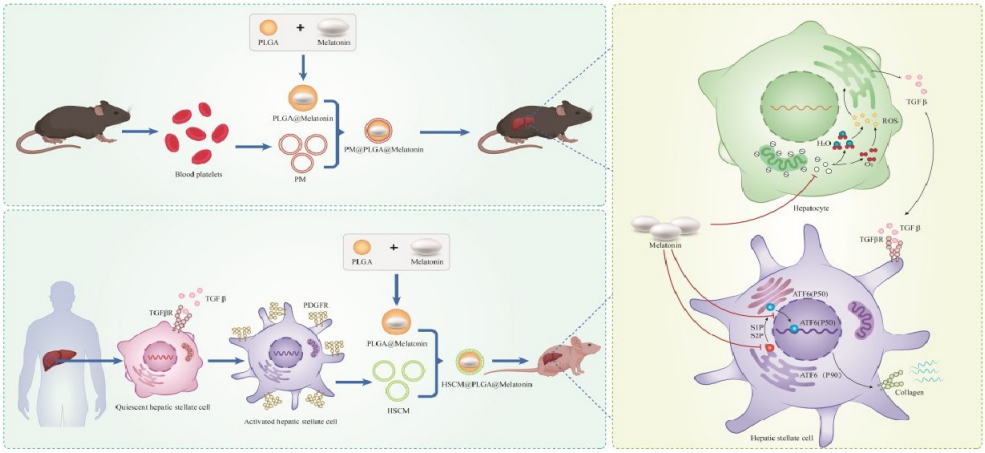

Figure 3. Schematic diagram of the role of functionalized nanoparticles in macrophage polarization and oxidative stress regulation

Bai Y, Chen J, Zhang S, Xu G, Mao Z, Ding Y, Wang W. Inflammation-Responsive Cell Membrane-Camouflaged Nanoparticles against Liver Fibrosis via Regulating Endoplasmic Reticulum Stress and Oxidative Stress. Adv Mater. 2024 May;36(19): e2310443. doi: 10.1002/adma.202310443. Epub 2024 Feb 26. PMID: 38372054.

Figure 3: Schematic diagram of the role of functionalized nanoparticles in regulating macrophage polarization and alleviating oxidative stress. The upper part of the figure shows that by combining nanoparticles (such as PLGA-methotrexate) with platelets, nanoparticles can precisely target and regulate macrophage polarization in mice, thereby reducing the inflammatory response. The lower part of the figure illustrates the mechanism of action of nanoparticles in the human body. Nanoparticles regulate macrophage polarization, inhibit the secretion of pro-inflammatory cytokines from M1 macrophages, and promote the anti-inflammatory function of M2 macrophages, effectively alleviating oxidative stress and inflammation. Through these mechanisms, functionalized nanoparticles not only reduce oxidative stress in osteoarthritis but also improve joint health.

In conclusion, functionalized nanoparticles regulate macrophage polarization, not only directly inhibiting inflammation but also reducing oxidative stress, improving the joint microenvironment, and ultimately alleviating osteoarthritis symptoms. This offers new strategies for the development of novel immune-modulatory therapies and drug delivery systems.

4.2 Promoting Cartilage Repair

The role of functionalized nanoparticles in osteoarthritis treatment extends beyond regulating inflammation and oxidative stress, as they also directly promote cartilage repair by influencing macrophage polarization. Cartilage degradation is one of the key pathological features of osteoarthritis, and damaged cartilage is difficult to repair on its own, presenting a significant challenge to osteoarthritis treatment [44]. Functionalized nanoparticles can effectively promote cartilage matrix regeneration and repair by improving the local microenvironment, regulating immune responses, and promoting the delivery of cartilage repair factors.

4.2.1 The Relationship Between Functionalized Nanoparticles, Macrophage Polarization, and Cartilage Repair

The key to cartilage repair lies in promoting the proliferation, differentiation, and matrix synthesis of chondrocytes while inhibiting the activity of destructive enzymes (such as MMP-13, ADAMTS-5). M2 macrophages play an important role in tissue repair by secreting anti-inflammatory cytokines (such as IL-10, TGF-β) to regulate the local immune environment, reduce the activity of destructive enzymes [45], and promote chondrocyte proliferation and matrix synthesis. Functionalized

nanoparticles can selectively promote M2 macrophage activity through the regulation of macrophage polarization, thereby enhancing the cartilage repair process.

Repair Role of M2 Macrophages:M2 macrophages promote tissue repair by secreting anti-inflammatory cytokines (such as IL-10, TGF-β, VEGF). IL-10 and TGF-β not only inhibit the activity of destructive enzymes such as MMP-13 but also stimulate chondrocyte proliferation and matrix synthesis [46]. Studies have shown that functionalized nanoparticles can target M2 macrophages to locally release anti-inflammatory cytokines, reducing inflammation while promoting cartilage matrix synthesis.

4.2.2 Direct Effects of Functionalized Nanoparticles on Chondrocytes

In addition to promoting cartilage repair through immune regulation, functionalized nanoparticles can also directly act on chondrocytes, activating repair-related signaling pathways to further promote cartilage repair.

TGF-β-loaded Nanoparticles: TGF-β is a key factor in cartilage repair. Functionalized nanoparticles loaded with TGF-β can directly act on chondrocytes, activating the Smad signaling pathway to promote chondrocyte proliferation, differentiation, and matrix synthesis [47]. Studies have shown that TGF-β-loaded nanoparticles significantly enhance chondrocyte proliferation and type II collagen deposition in cartilage defect models, promoting cartilage repair.

RNA Interference Technology: Functionalized nanoparticles can also use RNA interference technology to target and silence destructive genes (such as MMP-13, ADAMTS-5), directly reducing the activity of these enzymes and preventing the degradation of cartilage matrix [48]. For example, nanoparticles loaded with siRNA can significantly reduce cartilage matrix degradation by inhibiting MMP-13 expression, thereby promoting cartilage repair.

4.2.3 Role of Functionalized Nanoparticles in Bone Repair

Bone tissue repair is another critical issue in osteoarthritis treatment. Bone loss and insufficient bone repair are common problems during the progression of osteoarthritis, and the lack of bone tissue repair accelerates joint damage. Functionalized nanoparticles can effectively promote bone tissue repair by regulating macrophage polarization, improving the local microenvironment, and delivering osteogenic factors.

Delivery of Osteogenic Factors: Functionalized nanoparticles can effectively deliver osteogenic factors (such as BMP-2, VEGF) to activate the activity of bone marrow mesenchymal stem cells (BMSCs) and osteoblasts, promoting bone tissue regeneration. For example, BMP-2-loaded nanoparticles can significantly promote the generation of new bone tissue by targeting the delivery of BMP-2 [49], showing good bone repair effects in osteoarthritis animal models.

Hydroxyapatite Composite Nanoparticles: In addition, composite nanoparticles containing hydroxyapatite or calcium phosphate can simulate the bone matrix microenvironment, directly promoting the osteogenic differentiation of BMSCs. Research shows that these composite nanoparticles not only enhance the bone repair process but also regulate macrophage polarization, inducing M2 macrophages to secrete osteogenesis-related factors (such as VEGF, TGF-β) [50], further promoting the activity of osteoblasts.

5. Challenges and Prospects

5.1 Safety and Immunogenicity Issues of Functionalized Nanoparticles

Functionalized nanoparticles hold great promise in treatment but their safety and immunogenicity remain major challenges for clinical translation. Nanoparticles may trigger non-specific immune activation and toxic accumulation, especially synthetic materials (such as metal oxides), which may cause toxicity due to incomplete degradation. Natural polymer materials (such as hyaluronic acid) are ideal, but high doses may still cause local inflammation. Immunogenicity issues mainly arise from the binding of nanoparticles with serum proteins, which may reduce targeting effectiveness and

trigger acute inflammatory responses. Surface modifications (such as PEG) can optimize design to reduce immune responses and improve drug precision release.

5.2 Optimization of In vivo Targeting and Distribution

The targeting and distribution of nanoparticles directly affect therapeutic efficacy. Optimized designs, such as surface modifications with mannose or antibody fragments, can enhance targeting. The physicochemical properties of particles (such as size and surface charge) significantly influence targeting and distribution. Particles in the 50-200 nm range can effectively avoid kidney clearance and improve targeted delivery efficiency. Smart responsive designs (such as pH-responsive particles) can enhance local treatment effects. Real-time imaging technologies can track particle distribution, assisting in treatment monitoring and dose adjustment.

5.3 Future Research Directions and Challenges in Clinical Translation

Although functionalized nanoparticles show great potential in treating chronic diseases, challenges such as complex preparation processes, high costs, and personalized applications remain. Simplifying the production process and using microfluidic technologies can improve production efficiency and reduce costs. Personalized treatment requires optimizing nanoparticle design based on specific pathological features of patients. AI and big data analysis can assist in optimizing nanoparticle functionalization strategies based on patient characteristics. Clinical research will require multi-phase trials to validate safety, pharmacokinetics, and therapeutic efficacy. Regulatory approvals and market access for nanoparticles are also key to clinical translation and require cooperation with regulatory agencies to establish standardized processes for clinical applications.

6. Conclusion

Functionalized nanoparticles, by regulating macrophage polarization, show great potential in treating osteoarthritis. By targeting the delivery of anti-inflammatory molecules or directly regulating cellular signaling pathways, these nanoparticles can significantly reduce joint inflammation, improve the local microenvironment, and promote cartilage and bone tissue repair. Their multifunctional design not only enhances the precision and efficiency of treatment but also reduces systemic side effects, providing an innovative strategy for comprehensive osteoarthritis treatment.

As nanotechnology and medicine continue to integrate, functionalized nanoparticles open up new possibilities for treating chronic inflammatory diseases like osteoarthritis. Future research should focus on further optimizing nanoparticle design and addressing key issues in targeting, safety, and clinical translation. Through multidisciplinary collaboration and technological innovation, functionalized nanoparticles are expected to play a larger role in precision medicine, offering patients more efficient, safer, and personalized treatment options.

References

[1] Qiu S, Shi Y, Zang H, et al. Multifunctional injectable microspheres for osteoarthritis therapy via spatiotemporally modulating macrophage polarization and inflammation[J]. NPJ Regenerative Medicine, 2024, 9(1): 3.DOI:10.1038/s41536-024-00368-w.

[2] Yuan Z, Jiang D, Yang M, Tao J, Hu X, Yang X, Zeng Y. Emerging Roles of Macrophage Polarization in Osteoarthritis: Mechanisms and Therapeutic Strategies. Orthop Surg. 2024 Mar;16(3):532-550. doi: 10.1111/os.13993. Epub 2024 Jan 31. PMID: 38296798; PMCID: PMC10925521.

[3] Yao Z, Qi W, Zhang H, Zhang Z, Liu L, Shao Y, Zeng H, Yin J, Pan H, Guo X, Liu A, Cai D, Bai X, Zhang H. Down-regulated GAS6 impairs synovial macrophage efferocytosis and promotes obesity-associated osteoarthritis. Elife. 2023 May 5;12: e83069. doi: 10.7554/eLife.83069. PMID: 37144868; PMCID: PMC10191622.

[4] Pang L, Jin H, Lu Z, Xie F, Shen H, Li X, Zhang X, Jiang X, Wu L, Zhang M, Zhang T, Zhai Y, Zhang Y, Guan H, Su J, Li M, Gao J. Treatment with Mesenchymal Stem Cell-Derived Nanovesicle-Containing

Gelatin Methacryloyl Hydrogels Alleviates Osteoarthritis by Modulating Chondrogenesis and Macrophage Polarization. Adv Healthc Mater. 2023 Jul;12(17):e2300315. doi: 10.1002/adhm.202300315. Epub 2023 Mar 9. PMID: 36848378.

[5] Nedunchezhiyan U, Varughese I, Sun AR, Wu X, Crawford R, Prasadam I. Obesity, Inflammation, and Immune System in Osteoarthritis. Front Immunol. 2022 Jul 4;13:907750. doi: 10.3389/ fimmu. 2022. 907750. PMID: 35860250; PMCID: PMC9289681.

[6] Zou X, Xu H, Qian W. Macrophage Polarization in the Osteoarthritis Pathogenesis and Treatment. Orthop Surg. 2025 Jan;17(1):22-35. doi: 10.1111/os.14302. Epub 2024 Dec 5. PMID: 39638774; PMCID: PMC11735378.

[7] Fang C, Zhong R, Lu S, Yu G, Liu Z, Yan C, Gao J, Tang Y, Wang Y, Zhao Q, Feng X. TREM2 promotes macrophage polarization from M1 to M2 and suppresses osteoarthritis through the NF-κB/CXCL3 axis. Int J Biol Sci. 2024 Mar 11;20(6):1992-2007. doi: 10.7150/ijbs.91519. PMID: 38617547; PMCID: PMC11008261.

[8] Ko CY, Lin YY, Achudhan D, Chang JW, Liu SC, Lai CY, Huang YL, Tsai CH, Fong YC, Chen HT, Lee KT, Huang CC, Chang TK, Tang CH. Omentin-1 ameliorates the progress of osteoarthritis by promoting IL-4-dependent anti-inflammatory responses and M2 macrophage polarization. Int J Biol Sci. 2023 Oct 16;19(16):5275-5289. doi: 10.7150/ijbs.86701. PMID: 37928270; PMCID: PMC10620827.

[9] Liu B, Xian Y, Chen X, Shi Y, Dong J, Yang L, An X, Shen T, Wu W, Ma Y, He Y, Gong W, Peng R, Lin J, Liu N, Guo B, Jiang Q. Inflammatory Fibroblast-Like Synoviocyte-Derived Exosomes Aggravate Osteoarthritis via Enhancing Macrophage Glycolysis. Adv Sci (Weinh). 2024 Apr;11(14): e2307338. doi: 10.1002/advs.202307338. Epub 2024 Feb 11. PMID: 38342630; PMCID: PMC11005727.

[10] Wu CL, Harasymowicz NS, Klimak MA, Collins KH, Guilak F. The role of macrophages in osteoarthritis and cartilage repair. Osteoarthritis Cartilage. 2020 May;28(5):544-554. doi: 10.1016/j.joca.2019.12.007. Epub 2020 Jan 8. PMID: 31926267; PMCID: PMC7214213.

[11] Wang L, He C. Nrf2-mediated anti-inflammatory polarization of macrophages as therapeutic targets for osteoarthritis. Front Immunol. 2022 Aug 12; 13:967193. doi: 10.3389/fimmu.2022.967193. PMID: 360 32081; PMCID: PMC9411667.

[12] Sun H, Sun Z, Xu X, Lv Z, Li J, Wu R, Fei Y, Tan G, Liu Z, Liu Y, Shi D. Blocking TRPV4 Ameliorates Osteoarthritis by Inhibiting M1 Macrophage Polarization via the ROS/NLRP3 Signaling Pathway. Antioxidants (Basel). 2022 Nov 23;11(12):2315. doi: 10.3390/antiox11122315. PMID: 36552524; PMCID: PMC9774183.

[13] He XX, Huang YJ, Hu CL, Xu QQ, Wei QJ. Songorine modulates macrophage polarization and metabolic reprogramming to alleviate inflammation in osteoarthritis. Front Immunol. 2024 Feb 13; 15:1344949. doi: 10.3389/fimmu.2024.1344949. PMID: 38415250; PMCID: PMC10896988.

[14] Liu X, Ren X, Zhou L, Liu K, Deng L, Qing Q, Li J, Zhi F, Li M. Tollip Orchestrates Macrophage Polarization to Alleviate Intestinal Mucosal Inflammation. J Crohns Colitis. 2022 Aug 4;16(7):1151-1167. doi: 10.1093/ecco-jcc/jjac019. PMID: 35134154.

[15] Yang J, Li S, Li Z, Yao L, Liu M, Tong KL, Xu Q, Yu B, Peng R, Gui T, Tang W, Xu Y, Chen J, He J, Zhao K, Wang X, Wang X, Zha Z, Zhang HT. Targeting YAP1-regulated Glycolysis in Fibroblast-Like Synoviocytes Impairs Macrophage Infiltration to Ameliorate Diabetic Osteoarthritis Progression. Adv Sci (Weinh). 2024 Feb;11(5): e2304617. doi: 10.1002/advs.202304617. Epub 2023 Dec 3. PMID: 38044289; PMCID: PMC10837355.

[16] Wu B, Pan W, Luo S, Luo X, Zhao Y, Xiu Q, Zhong M, Wang Z, Liao T, Li N, Liu C, Nie C, Yi G, Lin S, Zou M, Li B, Zheng L. Turmeric-Derived Nanoparticles Functionalized Aerogel Regulates Multicellular Networks to Promote Diabetic Wound Healing. Adv Sci (Weinh). 2024 May;11 (18): e230 7630. doi: 10.1002/advs.202307630. Epub 2024 Mar 5. PMID: 38441389; PMCID: PMC11095230.

[17] Lu Q, Kou D, Lou S, Ashrafizadeh M, Aref AR, Canadas I, Tian Y, Niu X, Wang Y, Torabian P, Wang L, Sethi G, Tergaonkar V, Tay F, Yuan Z, Han P. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. J Hematol Oncol. 2024 Apr 2;17(1):16. doi: 10.1186/s13045-024-01535-8. PMID: 38566199; PMCID: PMC10986145.

[18] Zhou J, Liu W, Zhao X, Xian Y, Wu W, Zhang X, Zhao N, Xu FJ, Wang C. Natural Melanin/Alginate Hydrogels Achieve Cardiac Repair through ROS Scavenging and Macrophage Polarization. Adv Sci

(Weinh). 2021 Oct;8(20): e2100505. doi: 10.1002/advs.202100505. Epub 2021 Aug 19. PMID: 34414693; PMCID: PMC8529445.

[19] Li JM, Li X, Chan LWC, Hu R, Zheng T, Li H, Yang S. Lipotoxicity-polarised macrophage-derived exosomes regulate mitochondrial fitness through Miro1-mediated mitophagy inhibition and contribute to type 2 diabetes development in mice. Diabetologia. 2023 Dec;66(12):2368-2386. doi: 10.1007/s00125-023-05992-7. Epub 2023 Aug 24. PMID: 37615690.

[20] Bian F, Lan YW, Zhao S, Deng Z, Shukla S, Acharya A, Donovan J, Le T, Milewski D, Bacchetta M, Hozain AE, Tipograf Y, Chen YW, Xu Y, Shi D, Kalinichenko VV, Kalin TV. Lung endothelial cells regulate pulmonary fibrosis through FOXF1/R-Ras signaling. Nat Commun. 2023 May 4;14(1):2560. doi: 10.1038/s41467-023-38177-2. PMID: 37137915; PMCID: PMC10156846.

[21] Ding H, Zhang Y, Mao Y, Li Y, Shen Y, Sheng J, Gu N. Modulation of macrophage polarization by iron-based nanoparticles. Med Rev (2021). 2023 Apr 18;3(2):105-122. doi: 10.1515/mr-2023-0002. PMID: 37724082; PMCID: PMC10471121.

[22] Liu X, Fei H, Yang C, Wang J, Zhu X, Yang A, Shi Z, Jin X, Yang F, Wu D, Jiang L, Zhang S. Trophoblast-Derived Extracellular Vesicles Promote Preeclampsia by Regulating Macrophage Polarization. Hypertension. 2022 Oct;79(10):2274-2287. doi: 10.1161/ HYPERTENSIONAHA. 122. 19244. Epub 2022 Aug 22. PMID: 35993233.

[23] Liu X, Guo C, Yang W, Wang W, Diao N, Cao M, Cao Y, Wang X, Wang X, Pei H, Jiang Y, Kong M, Chen D. Composite microneedles loaded with Astragalus membranaceus polysaccharide nanoparticles promote wound healing by curbing the ROS/NF-κB pathway to regulate macrophage polarization. Carbohydr Polym. 2024 Dec 1; 345:122574. doi: 10.1016/j.carbpol.2024.122574. Epub 2024 Aug 6. PMID: 39227108.

[24] Zhao G, Xue L, Geisler HC, Xu J, Li X, Mitchell MJ, Vaughan AE. Precision treatment of viral pneumonia through macrophage-targeted lipid nanoparticle delivery. Proc Natl Acad Sci U S A. 2024 Feb 13; 121 (7): e2314747121. doi: 10.1073/pnas.2314747121. Epub 2024 Feb 5. PMID: 38315853; PMCID: PMC 10873611.

[25] Li H, Yuan Y, Zhang L, Xu C, Xu H, Chen Z. Reprogramming Macrophage Polarization, Depleting ROS by Astaxanthin and Thioketal-Containing Polymers Delivering Rapamycin for Osteoarthritis Treatment. Adv Sci (Weinh). 2024 Mar;11(9):e2305363. doi: 10.1002/advs.202305363. Epub 2023 Dec 14. PMID: 38093659; PMCID: PMC10916582.

[26] Xu L, Xing Z, Yuan J, Han Y, Jiang Z, Han M, Hou X, Xing W, Li Z. Ultrasmall Nanoparticles Regulate Immune Microenvironment by Activating IL-33/ST2 to Alleviate Renal Ischemia-Reperfusion Injury. Adv Healthc Mater. 2024 May;13(13):e2303276. doi: 10.1002/adhm.202303276. Epub 2024 Feb 21. PMID: 38335143.

[27] Zhang P, Miska J, Heimberger AB. GLUT3 regulates alternative macrophage signaling through a glucose transport-independent role. J Clin Invest. 2023 Nov 1;133(21):e174540. doi: 10.1172/JCI174540. PMID: 37909335; PMCID: PMC10617759.

[28] Deng, Q. S., Gao, Y., Rui, B. Y., Li, X. R., Liu, P. L., Han, Z. Y., Wei, Z. Y., Zhang, C. R., Wang, F., Dawes, H., Zhu, T. H., Tao, S. C., & Guo, S. C. (2023). Double-network hydrogel enhanced by SS31-loaded mesoporous polydopamine nanoparticles: Symphonic collaboration of near-infrared photothermal antibacterial effect and mitochondrial maintenance for full-thickness wound healing in diabetes mellitus. Bioactive materials, 27, 409–428. https://doi.org/10.1016/j.bioactmat.2023.04.004

[29] Ni C, Zhou J, Kong N, Bian T, Zhang Y, Huang X, Xiao Y, Yang W, Yan F. Gold nanoparticles modulate the crosstalk between macrophages and periodontal ligament cells for periodontitis treatment. Biomaterials. 2019 Jun;206:115-132. doi: 10.1016/j.biomaterials.2019.03.039. Epub 2019 Mar 25. PMID: 30933774.

[30] Han, X., Luo, R., Qi, S., Wang, Y., Dai, L., Nie, W., Lin, M., He, H., Ye, N., Fu, C., You, Y., Fu, S., & Gao, F. (2023). "Dual sensitive supramolecular curcumin nanoparticles" in "advanced yeast particles" mediate macrophage reprogramming, ROS scavenging and inflammation resolution for ulcerative colitis treatment. Journal of nanobiotechnology, 21(1), 321. https://doi.org/10.1186/s12951-023-01976-2

[31] He TR, Tang XY, Yan Q, Wu XY, Shi B, Lin Y. All-trans Retinoic Acid-incorporated Glycol Chitosan Nanoparticles Regulate Macrophage Polarization in Pg-LPS-Induced Inflammation. Curr Med Sci. 2022 Oct;42(5):974-980. doi: 10.1007/s11596-022-2602-8. Epub 2022 Oct 17. PMID: 36245026.

[32] Liu X, Ou X, Zhang T, Li X, Qiao Q, Jia L, Xu Z, Zhang F, Tian T, Lan H, Yang C, Kong L, Zhang Z. In situ neutrophil apoptosis and macrophage efferocytosis mediated by Glycyrrhiza protein nanoparticles for acute inflammation therapy. J Control Release. 2024 May; 369:215-230. doi: 10.1016/j. jconrel. 2024.03.029. Epub 2024 Mar 28. PMID: 38508529.

[33] Zhang M, Hu W, Cai C, Wu Y, Li J, Dong S. Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment. Mater Today Bio. 2022 Feb 21;14:100223. doi: 10.1016/ j. mtbio. 2022.100223. PMID: 35243298; PMCID: PMC8881671.

[34] Luo J, Zhang Y, Zhu S, Tong Y, Ji L, Zhang W, Zhang Q, Bi Q. The application prospect of metal/metal oxide nanoparticles in the treatment of osteoarthritis. Naunyn Schmiedebergs Arch Pharmacol. 2021 Oct;394(10):1991-2002. doi: 10.1007/s00210-021-02131-0. Epub 2021 Aug 20. PMID: 34415355; PMCID: PMC8486704.

[35] Ma JC, Luo T, Feng B, Huang Z, Zhang Y, Huang H, Yang X, Wen J, Bai X, Cui ZK. Exploring the translational potential of PLGA nanoparticles for intra-articular rapamycin delivery in osteoarthritis therapy. J Nanobiotechnology. 2023 Oct 4;21(1):361. doi: 10.1186/s12951-023-02118-4. PMID: 3779 4470; PMCID: PMC10548624.

[36] Liang H, Yan Y, Sun W, Ma X, Su Z, Liu Z, Chen Y, Yu B. Preparation of Melatonin-Loaded Nanoparticles with Targeting and Sustained Release Function and Their Application in Osteoarthritis. Int J Mol Sci. 2023 May 14;24(10):8740. doi: 10.3390/ijms24108740. PMID: 37240086; PMCID: PMC 10217911.

[37] Liu S, Zhang C, Zhou Y, Zhang F, Duan X, Liu Y, Zhao X, Liu J, Shuai X, Wang J, Cao Z. MRI-visible mesoporous polydopamine nanoparticles with enhanced antioxidant capacity for osteoarthritis therapy. Biomaterials. 2023 Apr; 295: 122030. doi: 10.1016/j.biomaterials.2023.122030. Epub 2023 Jan 31. PMID: 36758340.

[38] Zheng L, Zhao S, Li Y, Xu J, Yan W, Guo B, Xu J, Jiang L, Zhang Y, Wei H, Jiang Q. Engineered MgO nanoparticles for cartilage-bone synergistic therapy. Sci Adv. 2024 Mar 8;10(10):eadk6084. doi: 10.1126/sciadv. adk6084. Epub 2024 Mar 8. Erratum in: Sci Adv. 2024 Jul 19;10(29):eadr4798. doi: 10.1126/sciadv. adr4798. PMID: 38457498; PMCID: PMC10923500.

[39] Ma X, Luan Z, Li J. Inorganic Nanoparticles-Based Systems in Biomedical Applications of Stem Cells: Opportunities and Challenges. Int J Nanomedicine. 2023 Jan 7; 18:143-182. doi: 10.2147/IJN.S384343. PMID: 36643862; PMCID: PMC9833678.

[40] Liu X, Corciulo C, Arabagian S, Ulman A, Cronstein BN. Adenosine-Functionalized Biodegradable PLA-b-PEG Nanoparticles Ameliorate Osteoarthritis in Rats. Sci Rep. 2019 May 15;9(1):7430. doi: 10.1038/s41598-019-43834-y. PMID: 31092864; PMCID: PMC6520388.

[41] Chen H, Chen F, Hu F, Li Y, Zhang M, Zhou Q, Ding T, Tulufu N, Ye T, Wang F, Guo L. MicroRNA-224-5p nanoparticles balance homeostasis via inhibiting cartilage degeneration and synovial inflammation for synergistic alleviation of osteoarthritis. Acta Biomater. 2023 Sep 1;167:401-415. doi: 10.1016/j.actbio.2023.06.010. Epub 2023 Jun 15. PMID: 37330028.

[42] Wu H, Wang J, Lin Y, He W, Hou J, Deng M, Chen Y, Liu Q, Lu A, Cui Z, Guan D, Yu B. Injectable Ozone-Rich Nanocomposite Hydrogel Loaded with D-Mannose for Anti-Inflammatory and Cartilage Protection in Osteoarthritis Treatment. Small. 2024 Jun;20(25):e2309597. doi: 10.1002/smll.202309597. Epub 2024 Jan 26. PMID: 38279613.

[43] Park H, Lee HR, Shin HJ, Park JA, Joo Y, Kim SM, Beom J, Kang SW, Kim DW, Kim J. p16INK4a-siRNA nanoparticles attenuate cartilage degeneration in osteoarthritis by inhibiting inflammation in fibroblast-like synoviocytes. Biomater Sci. 2022 Jun 14;10(12):3223-3235. doi: 10.1039/d1bm01941d. PMID: 35579255.

[44] Rong M, Liu D, Xu X, Li A, Bai Y, Yang G, Liu K, Zhang Z, Wang L, Wang K, Lu L, Jiang Y, Liu J, Zhang X. A Superparamagnetic Composite Hydrogel Scaffold as In Vivo Dynamic Monitorable Theranostic Platform for Osteoarthritis Regeneration. Adv Mater. 2024 Aug;36(35):e2405641. doi: 10.1002/adma.202405641. Epub 2024 Jul 6. PMID: 38877353.

[45] Brady MA, Waldman SD, Ethier CR. The application of multiple biophysical cues to engineer functional neocartilage for treatment of osteoarthritis. Part II: signal transduction. Tissue Eng Part B Rev. 2015 Feb;21(1):20-33. doi: 10.1089/ten.TEB.2013.0760. Epub 2014 Oct 24. PMID: 25065615.

[46] Wu C, Huang Z, Chen J, Li N, Cai Y, Chen J, Ruan G, Han W, Ding C, Lu Y. Efficiently directing differentiation and homing of mesenchymal stem cells to boost cartilage repair in osteoarthritis via a nanoparticle and peptide dual-engineering strategy. Biomaterials. 2025 Jan; 312:122720. doi: 10.1016/j. biomaterials.2024.122720. Epub 2024 Jul 27. PMID: 39084098.

[47] Dos Santos Haupenthal DP, Resmini MB, Da Silva LA, Colares MC, de Roch Casagrande L, Milanez Venturini L, de Andrade TAM, do Bomfim FRC, Thirupathi A, Emilio Feuser P, Dal Pizzol F, Silveira PCL. Intra-articular Treatment with Triamcinolone Hexacetonide Associated with Gold Nanoparticles Reduces Cartilage Degeneration in an Animal Model of Osteoarthritis. Curr Drug Targets. 2023;24(3):287-296. doi: 10.2174/1389450124666221212090319. PMID: 36515017.

[48] Huang H, Yang L, He H, Zhou B, Qin Z, Zheng L, Shen C. Construction of mitochondrial-targeting nano-prodrug for enhanced Rhein delivery and treatment for osteoarthritis in vitro. Int J Pharm. 2024 Aug 15;661: 124397. doi: 10.1016/j.ijpharm.2024.124397. Epub 2024 Jun 28. PMID: 38945463.

[49] Li T, Guo M, Zhang W. Comparison of Therapeutic Effects of Topical Application of Diclofenac Sodium Nanoparticles and Conventional Placebo on Knee Osteoarthritis. Cell Mol Biol (Noisy-le-grand). 2022 Mar 31;68(3):171-178. doi: 10.14715/cmb/2022.68.3.20. PMID: 35988175.

[50] Zerrillo L, Gigliobianco MR, D'Atri D, Garcia JP, Baldazzi F, Ridwan Y, Fuentes G, Chan A, Creemers LB, Censi R, Di Martino P, Cruz LJ. PLGA Nanoparticles Grafted with Hyaluronic Acid to Improve Site-Specificity and Drug Dose Delivery in Osteoarthritis Nanotherapy. Nanomaterials (Basel). 2022 Jun 30;12(13):2248. doi: 10.3390/nano12132248. PMID: 35808084; PMCID: PMC9268068.

[51] Mayorga C, Perez-Inestrosa E, Rojo J, Ferrer M, Montañez MI. Role of nanostructures in allergy: Diagnostics, treatments and safety. Allergy. 2021 Nov;76(11):3292-3306. doi: 10.1111/all.14764. Epub 2021 Mar 9. PMID: 33559903.

[52] Liu F, Mao K, Chen H, Cong X, Tan H, Xin Y, Wang X, Ke J, Song Y, Yang YG, Sun T. Enhancing the Safety and Efficacy of Trastuzumab Emtansine (T-DM1) Through Nano-Delivery System in Breast Cancer Therapy. Small. 2024 Dec;20(50):e2400977. doi: 10.1002/smll.202400977. Epub 2024 Oct 6. PMID: 39370652.

[53] Ho TL, Mutalik C, Rethi L, Nguyen HT, Jheng PR, Wong CC, Yang TS, Nguyen TT, Mansel BW, Wang CA, Chuang EY. Cancer-targeted fucoidan-iron oxide nanoparticles for synergistic chemotherapy/ chemodynamic theranostics through amplification of P-selectin and oxidative stress. Int J Biol Macromol. 2023 Apr 30; 235: 123821. doi: 10.1016/j.ijbiomac.2023.123821. Epub 2023 Mar 2. PMID: 36870633.

[54] Zhang J, Liu S, Wang Y, Li X, Zeng H, Li B, Wang J. Preparation of Chitosan Nanoparticles through a Readily Solvent-Exchange Process for Efficient and Enhanced Gene Delivery. Langmuir. 2024 May 21;40(20):10486-10491. doi: 10.1021/acs.langmuir.3c03874. Epub 2024 May 10. PMID: 38728233.

[55] Di Felice G, Colombo P. Nanoparticle-allergen complexes for allergen immunotherapy. Int J Nanomedicine. 2017 Jun 19;12: 4493-4504. doi: 10.2147/IJN.S134630. PMID: 28684909; PMCID: PMC 5484593.

[56] Shmueli RB, Bhise NS, Green JJ. Evaluation of polymeric gene delivery nanoparticles by nanoparticle tracking analysis and high-throughput flow cytometry. J Vis Exp. 2013 Mar 1;(73): e50176. doi: 10.3791/50176. PMID: 23486314; PMCID: PMC3622088.

[57] Eloy JO, Petrilli R, Trevizan LNF, Chorilli M. Immunoliposomes: A review on functionalization strategies and targets for drug delivery. Colloids Surf B Biointerfaces. 2017 Nov 1; 159:454-467. doi: 10.1016/j. colsurfb. 2017. 07.085. Epub 2017 Aug 5. PMID: 28837895.